Diabetic Nephropathy
Why & why not ?

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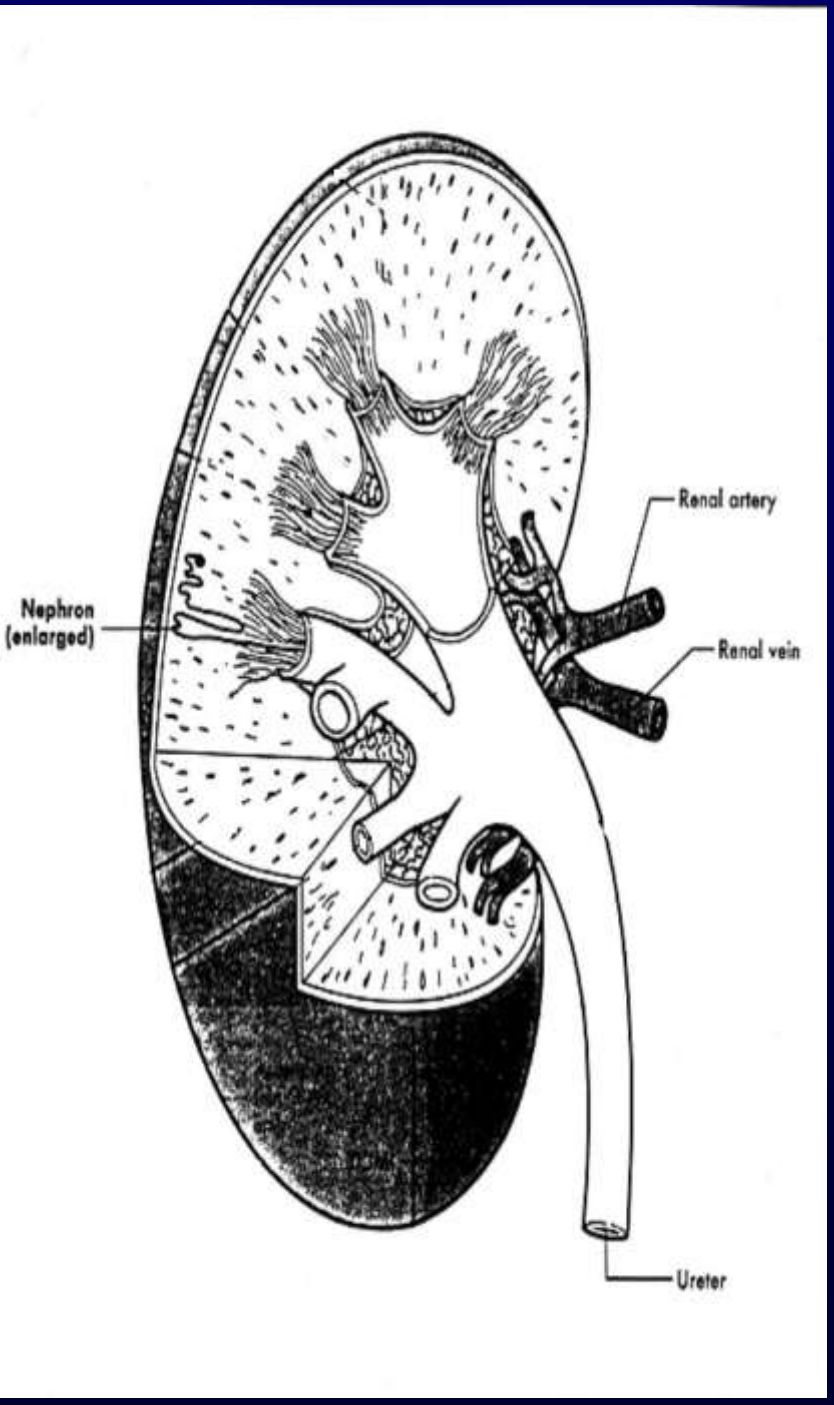
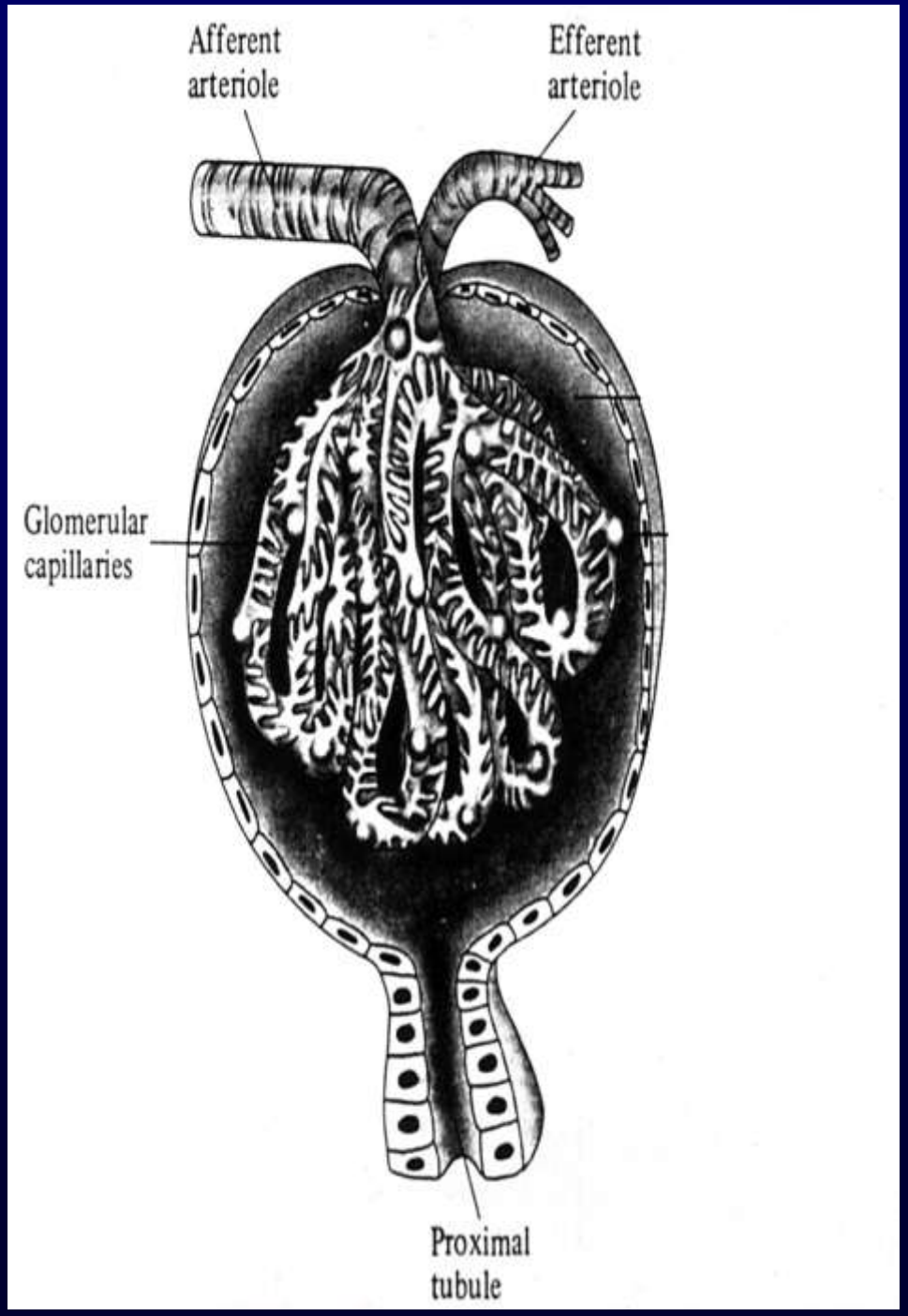
Are Some Diabetics Immune Against Diabetic Nephropathy ??


Renal artery
Nephron
(enlarged)
Renal vein
Ureter


Afferent
arteriole
Efferent
arteriole
Glomerular
capillaries
Proximal
tubule

Definition

- A microvascular complication of diabetes marked by albuminuria and a deteriorating course from normal renal function to ESRD.

Albuminuria 30 - 300 mg/day got called

"Microalbuminuria"

- it predicts the development of clinical nephropathy
- one "positive" is not enough in the low range
- detected by measuring the albumin/creatinine ratio on a spot urine sample

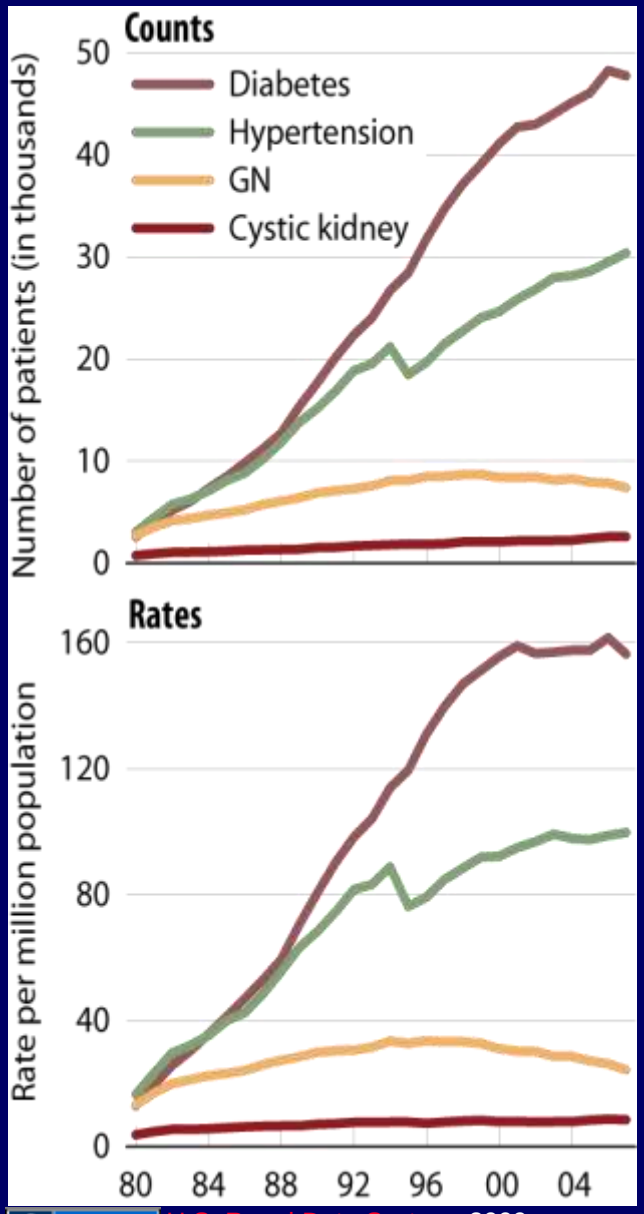
Epidemiology

- Diabetic nephropathy is the leading cause of ESRD in the US.
- It accounts for 43% of all patients on dialysis
- Cost to Medicare > $ 2 billion per year

- 63% of patients with diabetic nephropathy have type II DM
- The risk of developing diabetic nephropathy is not constant over the duration of diabetes

- About 20-30% of patients with type I DM develop microalbuminuria, less than half progress to overt nephropathy
- Incidence of ESRD is 16% at 30 years.
- 5-60% of type II DM patients develop DN, depending on ethnicity

Diabetes is the dominant cause of ESRD in USA



Incident ESRD patients; Medical Evidence form data; rates adjusted for age, gender, & race.

 U.S. Renal Data System, 2009

USRDS 2009

Epidemiology

Diabetic nephropathy affects approximately one third of people with type 1 or type 2 diabetes mellitus.

Increase prevalence of DM

USA

4% 1995 – 5.4% 2025

Now: USA 7% (20.8 million)

Worldwide:

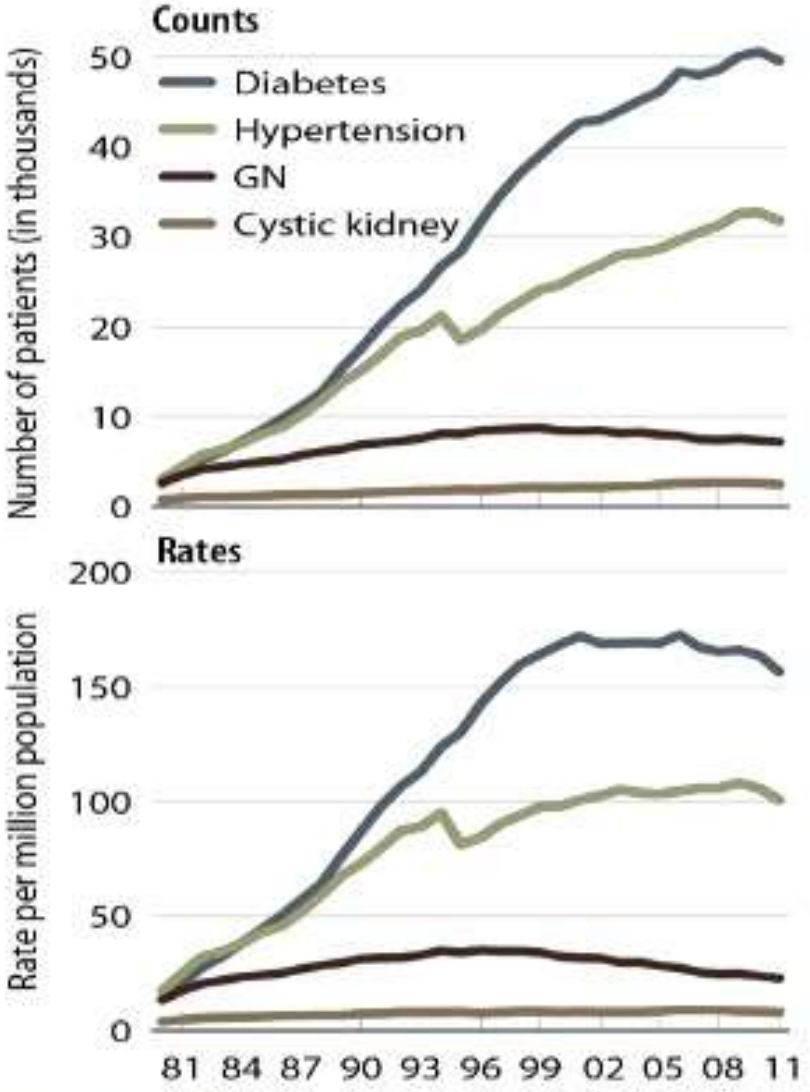
2.8 % 171 million 2000 –

4.4% 366 million 2030

DN prevalence

In India: 5.5% and 8.9%

Asian Indians in UK 22.3%

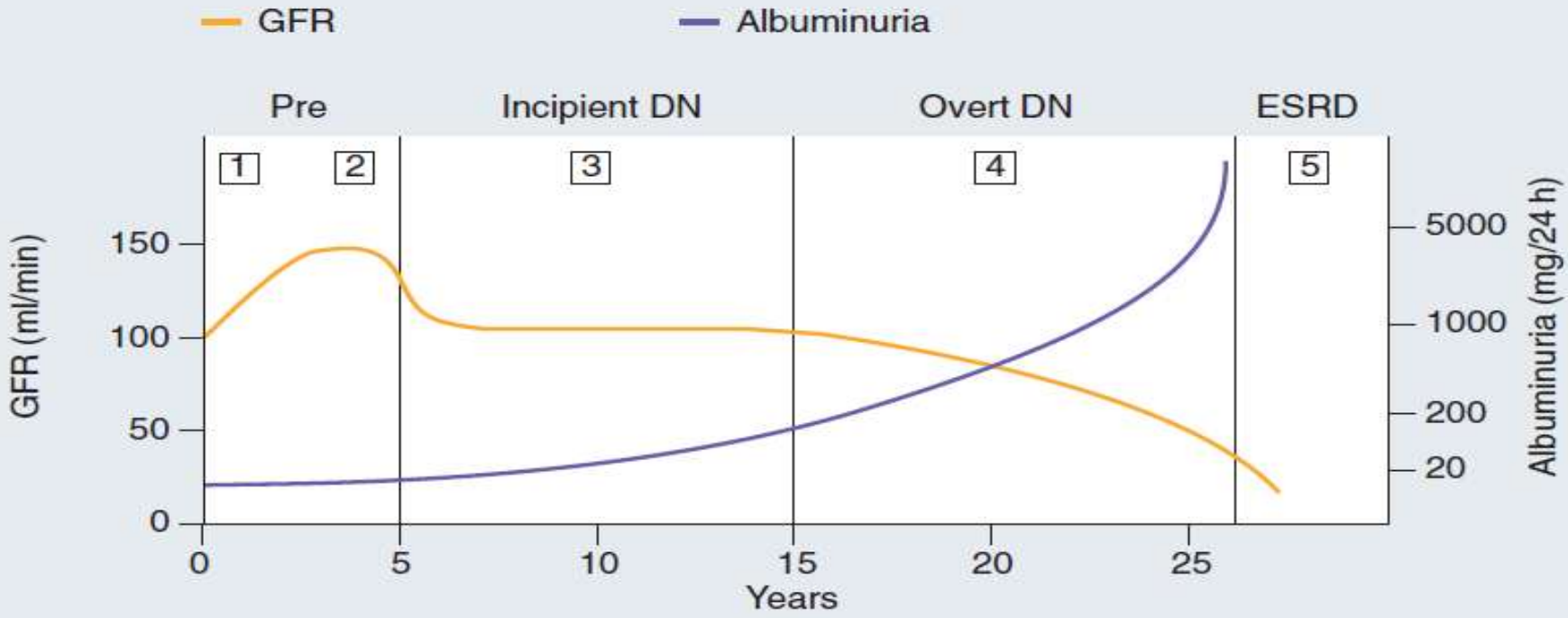


Incident ESRD patients.
Adj: age/gender/race; ref: 2010 ESRD patients.

Burden of diabetic nephropathy

- The rates of hospitalization for all causes are about three times higher in patients with CKD than in those who do not have the disease.
- patients with T2DM with DN and PAD are 1.2 to 1.3 times more likely to be hospitalized.
- ESRD is associated with increased mortality, mainly due to C.V. causes
- Reduced renal function is by itself an indicator of high mortality.
- Other concomitant risk factors such as hypertension and autonomic neuropathy can contribute to cardiovascular diseases
- Even patients with DN initially characterized by microalbuminuria already have an increased risk for CVD and higher mortality

Natural History of DKD



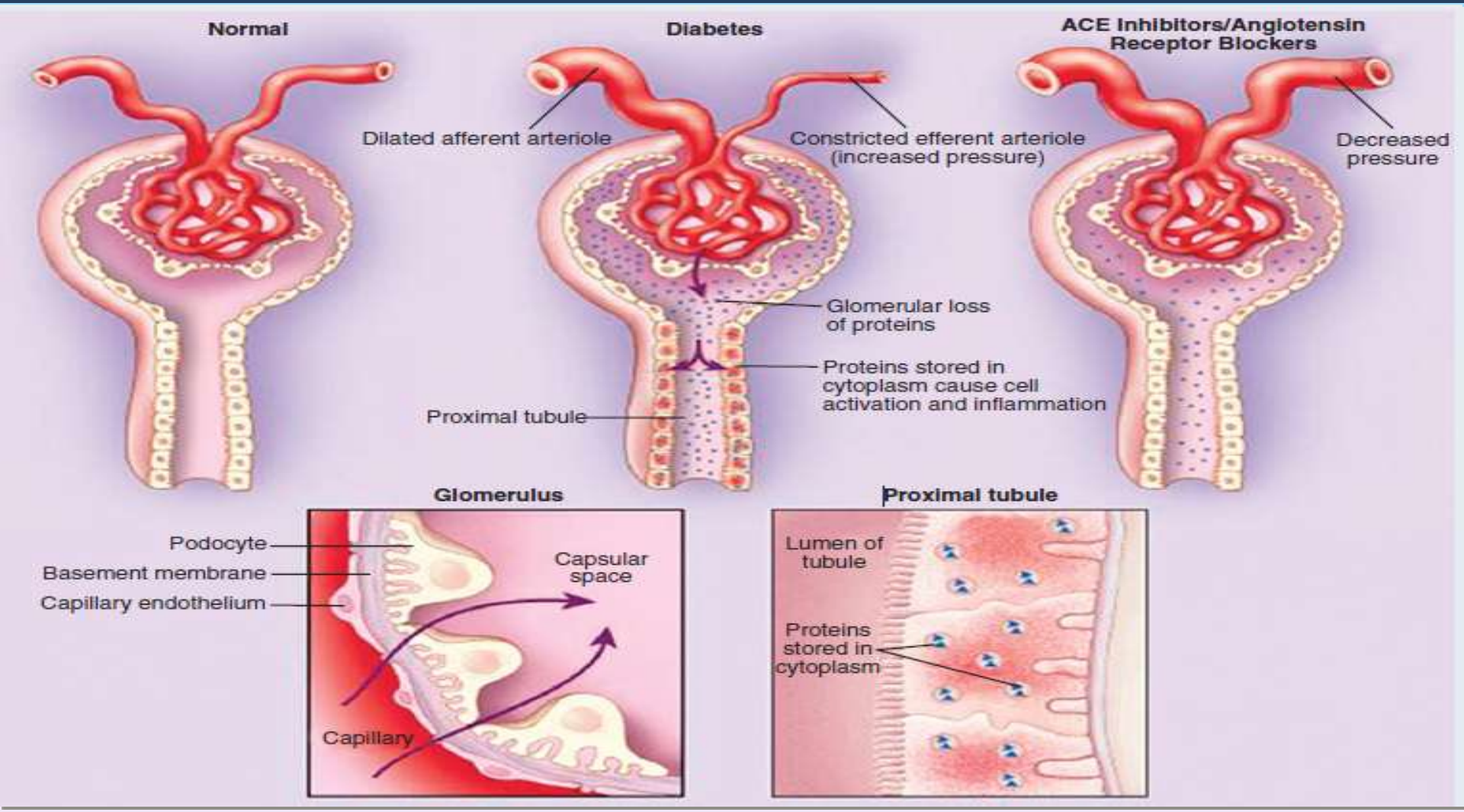
Stage	Pre	Incipient	Overt
Functional	GFR ↑ (25%–50%)	Microalbuminuria, hypertension	Proteinuria, nephrotic syndrome, GFR ↓
Structural	Renal hypertrophy	Mesangial expansion, GBM thickening, arteriolar hyalinosis	Mesangial nodules (Kimmelstiel-Wilson lesions) Tubulointerstitial fibrosis

Comprehensive textbook of Nephrology, 2010

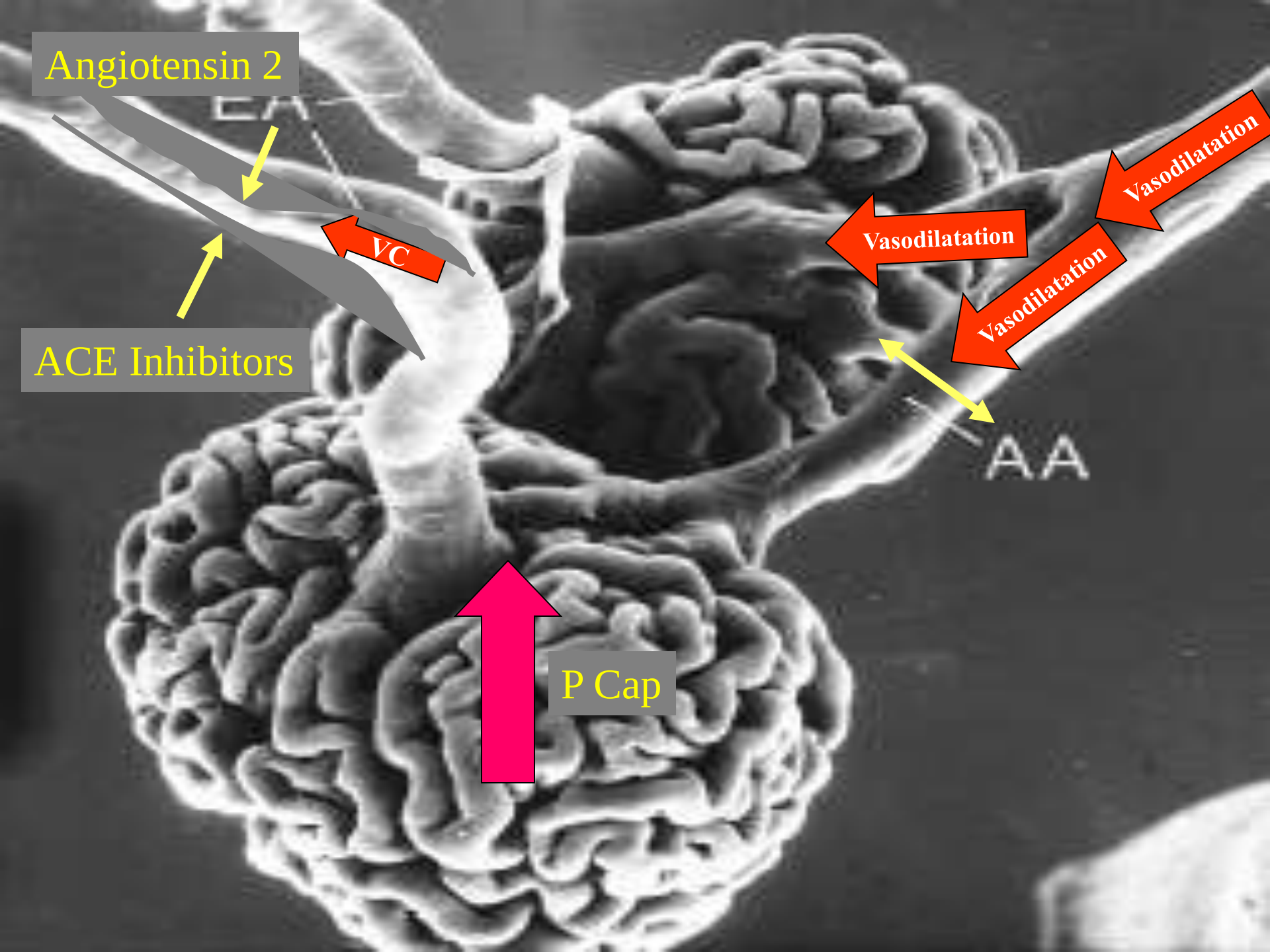
Pathology

- Expansion of mesangial matrix with diffuse and nodular glomerulosclerosis (Kimmelstiel-Wilson nodules)
- Thickening of glomerular and tubular BM
- Arteriosclerosis and hyalinosis of afferent and efferent arterioles
- Tubulointerstitial fibrosis

Nephron in DKD



Comprehensive textbook of Nephrology, 2010


Angiotensin 2
ACE Inhibitors
VC
Vasodilatation
Vasodilatation
Vasodilatation
AA
P Cap

Pathogenesis

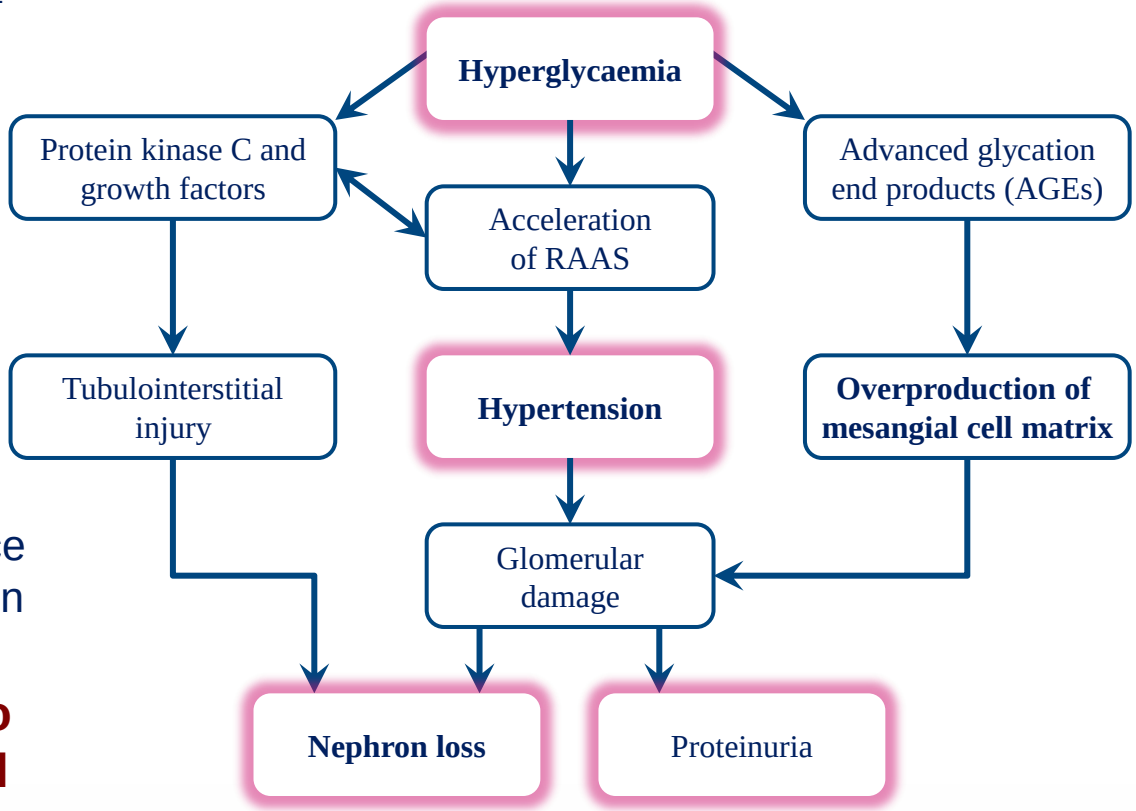
- Hyperglycemia
  - Induce mesangial expansion and injury
  - Increased activity of growth factors
  - Activation of cytokines
  - Formation of ROS
  - accumulation of advanced glycosylation endproducts in tissues
- Accumulation of ECM components, such as collagen

Hyperglycaemia drives diabetic kidney disease

Three mechanisms have been postulated that explain how hyperglycaemia causes tissue damage in the kidney:[1-3]

1. Activation of protein kinase C[1]
2. Acceleration of the renin-angiotensin-aldosterone system (RAAS)[1]
3. Non-enzymatic glycation that generates advanced glycation end products[1]
   - Circulating levels are raised in people with diabetes, particularly those with renal insufficiency, since they are normally excreted in the urine[1]

- **Oxidative stress seems to be a theme common to all three pathways[3]**



Reference:
1.Cade WT. Diabetes-Related Microvascular and macrovascular diseases in the physical therapy setting. Phys Ther. 2008;88(11):1322–1335. 2.Wolf G et al. (2005) From the periphery of the glomerular capillary wall toward the center of disease: podocyte injury comes of age in diabetic nephropathy. Diabetes 54: 1626-1634. 3.Dronavalli S, Duka I and Bakris GL. Nat Clin Pract Endocrinol Metab. 2008;4(8):444-52.

Urinary biomarkers of glomerular damage

**Increased permeability to plasma proteins (transferrin,albumin)

- Decreased glomerular charge selectivity
- Decreased glomerular size selectivity
- Increased intraglomerular pressure

** Increased excretion of extracellular matrix proteins(Type 4 collagen, fibronectin)

Urinary biomarkers of tubular damage

- **Inability of tubules to absorb filtered proteins:**

***Proximal tubular:**

-L-FAB

-Adiponectin (also glomerular markers)

-KIM-1

***Loop of Henle:**

-Osteopontin

***Distal tubular:**

-H-FABP

Pathogenesis

- Genetic predisposition to or protection from diabetic nephropathy
  - Differences in prevalence of microalbuminuria, ESRD in different patient populations
  - Only half of patients with poor glycemic control will develop diabetic nephropathy
  - Family studies
- Multiple genes may be involved

Why Incidence differ from patient to another ?

- About 20% to 30% of patients with type 1 and type 2 DM develop DN; however, a smaller proportion of patients with type 2 DM will progress to end-stage renal disease (ESRD).
- Due to its high prevalence, the majority of patients requiring dialysis are type 2 DM .
- but not all diabetic individuals will develop this complication ,Those who do not develop DN in the first 15 years after disease onset seem to be genetically protected.

Cont.

- Many environmental factors have been established as contributing to the development of DN while the role of others has yet to be clearly understood .
- **It is known that factors such as hyperglycemia, arterial hypertension and/or dyslipidemia play a role in the development of DN in genetically predisposed individuals only.**

Different Risk factors also affect incidence rate

- Hypertension
- Hyperglycemia
- Microalbuminuria
- Ethnicity
- Male gender
- Family history
- Cigarette smoking
- Dyslipidemia

- The interest in **identification of modifiable risk factors** of declining renal function is increasing.
- Such risk factors may be used to estimate a subject's risk of future declining renal function and may also form the basis for preventive intervention

Different Risk factors also affect incidence rate

- Hypertension
- Hyperglycemia
- Microalbuminuria
- Ethnicity
- Male gender
- Family history
- Cigarette smoking
- Dyslipidemia

see commentary on page 415

Gender differences in predictors of the decline of renal function in the general population

Nynke Halbesma[1], Auke H. Brantsma[1], Stephan J.L. Bakker[1], Desiree F. Jansen[2], Ronald P. Stolk[2], Dick De Zeeuw[3], Paul E. De Jong[1] and Ronald T. Gansevoort[1] for the PREVEND study group

[1]Division of Nephrology, Department of Medicine, University Medical Center Groningen (UMCG), University of Groningen, Groningen, The Netherlands; [2]Department of Epidemiology, University Medical Center Groningen (UMCG), University of Groningen, Groningen, The Netherlands and [3]Department of Clinical Pharmacology, University Medical Center Groningen (UMCG), University of Groningen, Groningen, The Netherlands

5488 participants of the prospective, community-based cohort study PREVEND who completed three visits during a mean follow-up of 6.5 years.

The change in renal function was used as the outcome and this was calculated as the linear regression of three estimated GFR measurements obtained during follow-up.

Risk factors, known to influence renal outcome in patients with primary renal diseases, were used as potential predictors in multivariate regression analyses.

Renal function decline is observed in the higher range of **Blood glucose** both in males and in females.

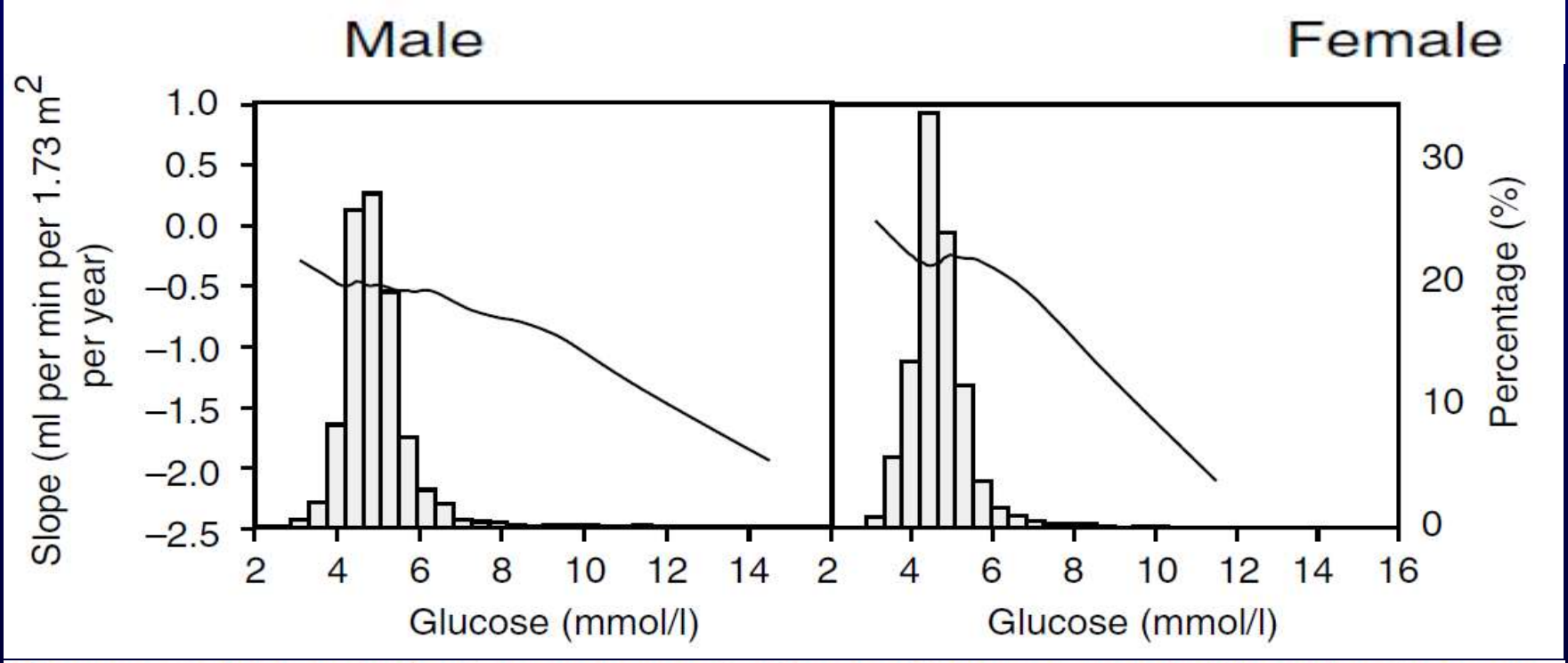


Figure 1 | Graphical representation of the association between risk predictors and change in renal function during follow-up (assessed as slope through three eGFR values over time per individual).

Renal function decline is observed in the higher range of **Systolic Blood Pressure** both in males and in females.

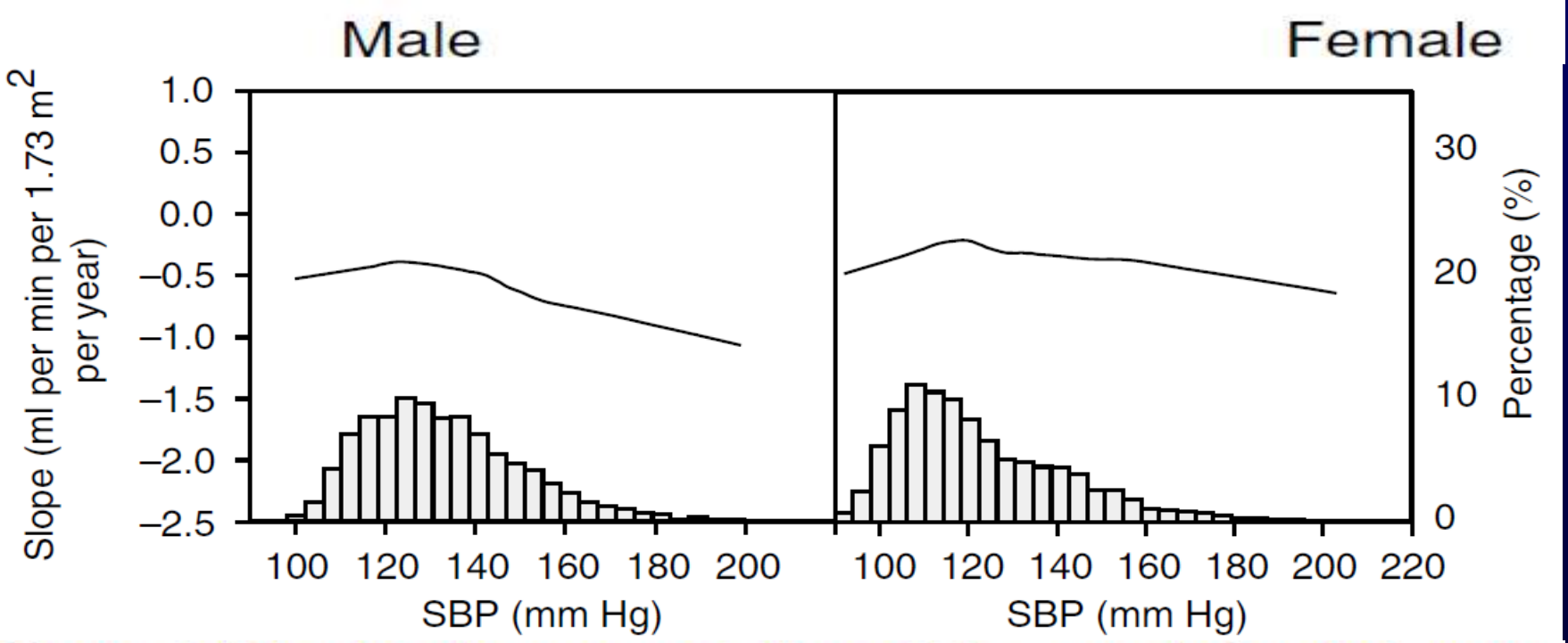


Figure 2 | Graphical representation of the association between risk predictors and change in renal function during follow-up (assessed as slope through three eGFR values over time per individual).

Renal function decline is observed in the higher range of **Urine Albumin Excretion**, both in males and in females.

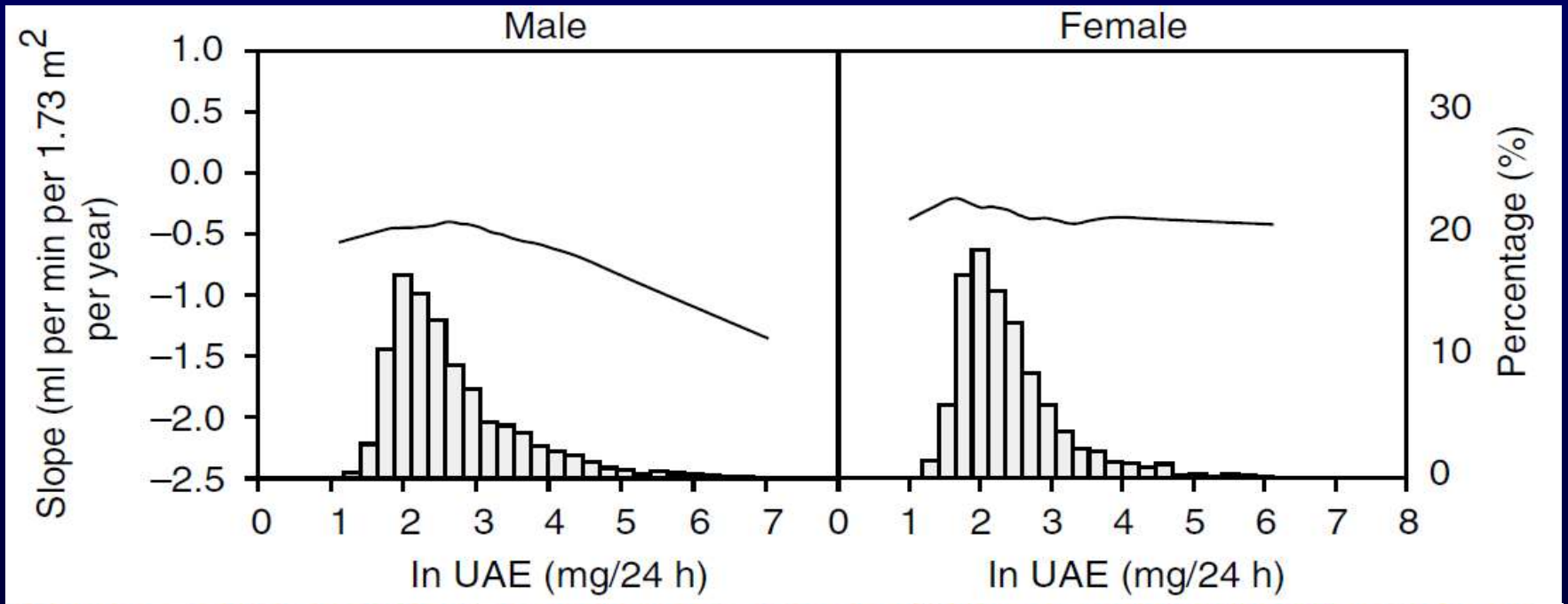


Figure 3 | Graphical representation of the association between risk predictors and change in renal function during follow-up (assessed as slope through three eGFR values over time per individual).

Conclusion of Gender difference

High systolic blood pressure and plasma glucose were found to be independent predictors for an accelerated decline in function for both genders.

In males, albuminuria was the strongest independent predictor for renal function decline, whereas in females albuminuria was univariately associated only after adjustment for age.

The direction of the association between cholesterol/HDL ratio and decline of renal function differed by gender.

Surprisingly,in males, waist circumference was an independent predictor and positively associated with renal function outcome.

These studies show that there are gender differences in the standard predictors of the decline in renal function

Gender differences in chronic kidney disease

Kunitoshi Iseki[1]

Women live longer than men. Can this phenomenon be explained by chronic kidney disease (CKD)? Gender differences in the prevalence and incidence of CKD are discussed.

Kidney International (2008) **74**, 415–417. doi:10.1038/ki.2008.261

- Gender differences have been documented in the field of nephrology.
- Women seem to be somewhat protected from developing ESRD.
- The cumulative incidence of ESRD remains low during the reproductive ages and begins to rise 10 years later in women than in men among participants in community-based screenings

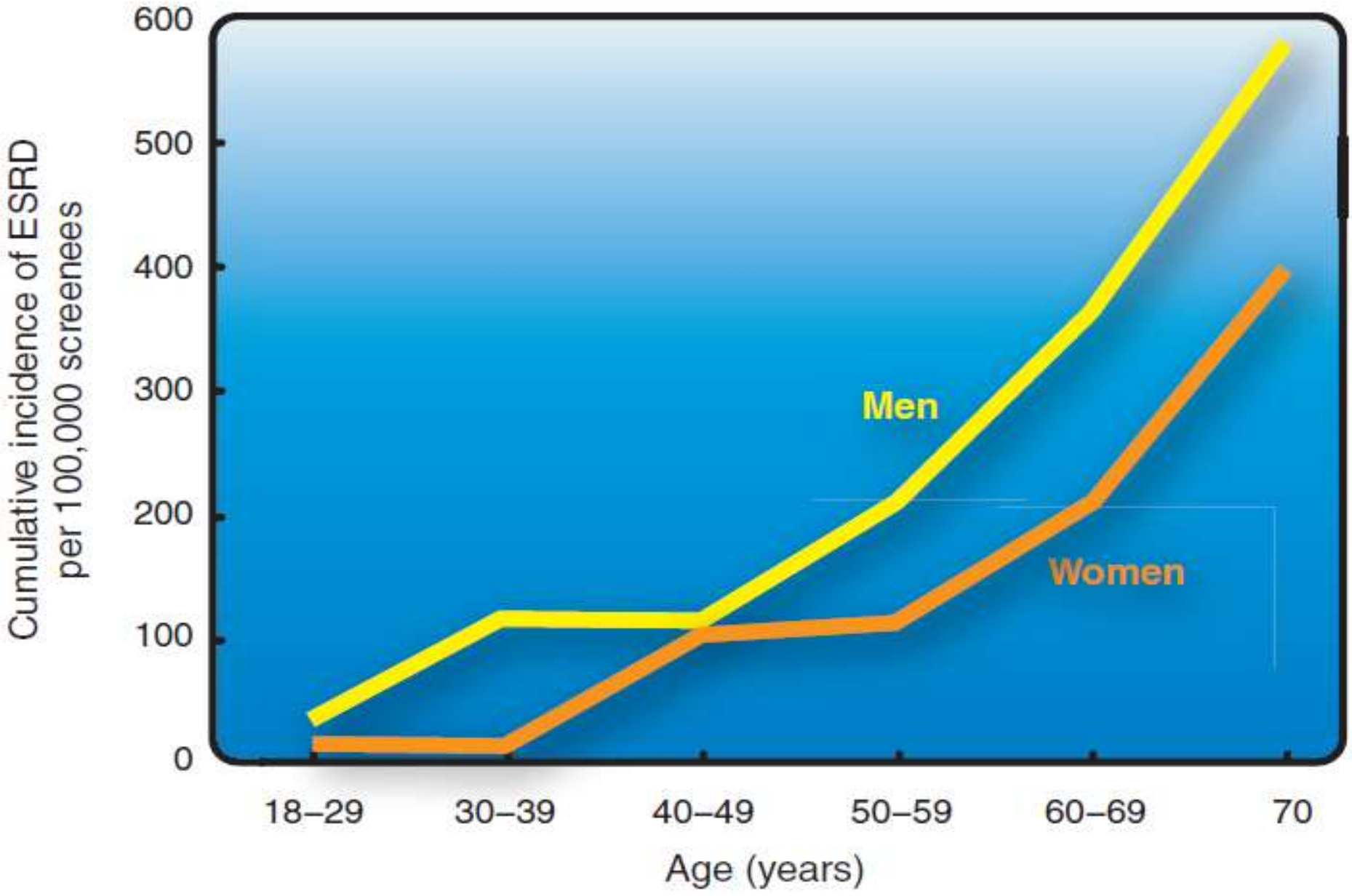
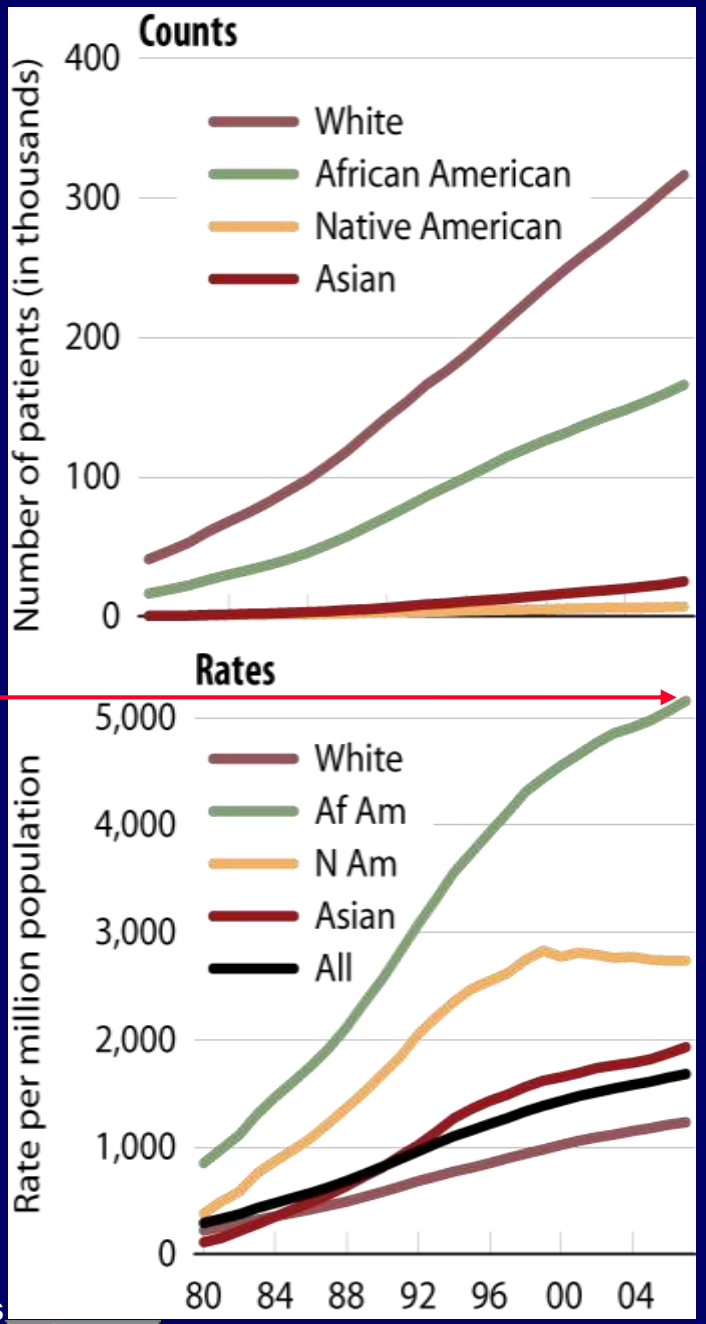


Figure 1 | The cumulative incidence of ESRD per 100,000 screenees, shown by age at screening in both men and women.

Race (non modifiable risk factor)

Diabetes is the dominant cause of ESRD in USA …more so in AAs



December 31 point prevalent ESRD patients; rates adjusted for age & gender.

 U.S. Renal Data System, 2009

USRDS 2009

World Journal of Diabetes

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4239/wjd.v6.i5.759

World J Diabetes 2015 June 10; 6(5): 759-773
ISSN 1948-9358 (online)

SYSTEMATIC REVIEWS

Diabetic nephropathy in Africa: A systematic review

- **Methods:**

  Meta-Analysis and Systematic Reviews of Observational Studies, between January 1994 and July 2014 ,of each of the 54 African countries and African sub-regions to capture the largest number of studies, reported on the prevalence, incidence or determinants of chronic kidney disease (CKD) in people with diabetes within African countries.

- Methods for assessing and classifying CKD varied widely. Measurement of urine protein was the most common method of assessing kidney damage (62.5% of studies).

Results:

- The overall prevalence of CKD varied from 11% to 83.7%.

- Incident event rates were
  94.9% for proteinuria at 10 years of follow-up,
  34.7% for endstage renal disease at 5 years of follow-up and
  18.4% for mortality from nephropathy at 20 years of follow up.

- Duration of diabetes, blood pressure, advancing age, obesity and glucose control were the common determinants of kidney disease.

Table 3 Prevalence and incidence of chronic kidney disease in people with diabetes across studies in Africa

Ref.	Country	Sample size	Type of diabetes	Duration of follow-up	Diagnostic criteria for CKD	Prevalence	Incidence	Comments
Motala *et al*[37], 2001	South Africa	219	T1DM and T2DM	16.10 (4.9) T1DM; 18.6 (5.7) T2DM; at least 10 yr	Persistent proteinuria (dipstix proteinuria on three or more consecutive occasions over 18 mo in the at absence of infection or cardiac failure)	Not applicable	24.6%	
Elbagir *et al*[26], 1995	Sudan	128	Insulin-treated	Not applicable	Proteinuria (≥ 30 mg/dL)	22%	Not applicable	
Sobngwi *et al*[44], 1999	Cameroon	64	T1DM and T2DM	Not applicable	Proteinuria	53.1%	Not applicable	
Katchunga *et al*[30], 2010	DR Congo	98	T2DM	Not applicable	MDRD: CKD stage ≥ 2 according to the National Kidney foundation	18.1%	Not applicable	
Choukem *et al*[22], 2012	Cameroon	420	T2DM	Not applicable	Proteinuria (30 mg/24 h)	31%	Not applicable	
Keeton *et al*[31], 2004	South Africa	59	T2DM	12 yr	Urine Albumin-to-Creatinine Ratio (no detail)		After 12 yr of follow-up or death, 94.9% (56/59) had a proteinuria with a mean duration from diabetes onset to proteinuria of 9.7 (5.9) yr	83% (49/59) had an elevated SCr at the end of the study and in 66.1% (39/59) the SCr level had doubled during the study

Pruijm *et al*[39], 2008	Seychelles	1218	All types	Not applicable	Microalbuminuria: Urine Albumin-to-Creatinine Ratio 3.4-33.9 mg albumin/mmol creatinine	36.1%	Not applicable	
Alebiosu[16], 2003	Nigeria	342	T1DM and T2DM	Not applicable	Persistent proteinuria	28.4%	Not applicable	
Bouaziz *et al*[20], 2012	Tunisia	73	T2DM	Not applicable	Microalbuminuria: < 2.8 g/mol for women and < 2.3 g/mol for men	11%	Not applicable	
Ajayi *et al*[15], 2014	Nigeria	65	T2DM	Not applicable	MDRD: eGFR $\leqslant$ 60 mL/min per 1.73 m^2	43.1%	Not applicable	
Levitt *et al*[32], 1997	South Africa	243	T2DM and T1DM	Not applicable	Urine Albumin-to-Creatinine Ratio > 3.4 mm/mmol Persistent proteinuria (for at least 3 consecutive visits)	36.7% 5.3%	Not applicable	
Majaliwa *et al*[34], 2007	Tanzania	99	T1DM	Not applicable	Proteinuria (no detail)	29.3%	Not applicable	
Marshall *et al*[36], 2013	Rwanda	286	T1DM	Not applicable	Microalbuminuria: Urine Albumin-to-Creatinine Ratio = 30-299 mg/g Macroalbuminuria or overt nephropathy: Urine Albumin-to-Creatinine Ratio $\geqslant$ 300 mg/g	Microalbuminuria: 21%; Macroalbuminuria: 5%	Not applicable	
Alebiosu *et al*[16], 2003	Nigeria	465	T2DM	Not applicable	Proteinuria and eGFR	41.1%	Not applicable	The method for the estimation of the GFR is not indicated
Gill *et al*[28], 2005	South Africa	88	T1DM	20 yr	Persistent dipstick proteinuria		Death of renal cause after 20 yr = 18.4% (9/49)	Death due to chronic renal failure after 20 yr of follow-up was 9/49 (after exclusion of lost to follow)

Genetics of diabetic nephropathy

Bases genéticas da nefropatia diabética

Mariana P. Carpena[1], Dimitris V. Rados[1], Denise A. Sortica[1], Bianca M. de Souza[1], André Fernandes Reis[3], Luis Henrique Canani[1,2], Daisy Crispim[1,2]

Arq Bras Endocrinol Metab. 2010;54/3

Genetic differences in Nephropathy

GENETIC TRANSMISSION MODELS

- The genetic transmission mode of DN is still controversial. Theoretically, as in other diseases, it might occur in three distinct forms, which would lead to the development of DN.

Monogenic form	Oligogenic form	Polygenic form
mutations in a gene with a dominant role.	mutations/polymorphisms in a few genes would contribute in an independent and cumulative manner to increase susceptibility.	alterations in many DNA loci, and each would have a small and cumulative effect on DN development.

EVIDENCE FOR GENETIC PREDISPOSITION TO Diabetic Nephropathy

Familial aggregation of diabetic nephropathy

- Studies of familial aggregation have showed that some families are predisposed to DN .
- Studies on siblings with type 1 or type 2 DM have reported that DN in one of the siblings is associated with around a 3- to 4-fold increase in the risk of DN in the other sibling .
- There appears to be a genetic inheritance contributing to the development of CKD and showed that the heritability (h2) of UAE rate is approximately 30% when analyzing non-diabetic children of type 2 diabetic individuals

EVIDENCE FOR GENETIC PREDISPOSITION TO Diabetic Nephropathy

Familial aggregation of diabetic nephropathy

- Another study, showed that adjustment for covariables such as sex, age, obesity and DM, approximately 30% of the variability of albumin/creatinine rate was due to genetic factors
- The magnitude of the familial association cannot be attributed only to exposure to similar risk factors, suggesting there is a genetic component

Genes associated with diabetic nephropathy and different phenotypes

- Although proteinuria and loss of renal function often occur concomitantly, there is evidence of different genetic, some patients may have persistent proteinuria without progressing to loss of renal function and other patients have loss of renal function without proteinuria or microalbuminuria

Genome-wide scan studies

- **Recent GWS studies have demonstrated chromosomal regions potentially associated with DN.**

Genome-wide scan studies for genes associated with diabetic nephropathy

Author	Population studied	Regions associated	Phenotype
Imperatore and cols., 1998 (54)	Pima Indians- 98 siblings with DM2, concordant for ND	7q, 3 and 20	Albuminuria or proteinuria
Vardarli and cols., 2002 (55)	125 patients with DM2	18q22.3-23	Albuminuria
Tanaka and cols., 2003 (56)	Japanese with DM2 grouped into cases (with DR and DN) and controls (with DR and without DN)	16q13	Albuminuria
Bowden and cols., 2004 (57)	266 siblings with DM2, African-Americans, concordant for DN	3q, 7p and 18q	CKD
Krolewski and cols., 2006 (58)	59 Caucasian families, 1 African-American, and 3 Hispanic. Members with and without DM2	22q, 5q and 7q	Albuminuria
Iyengar and cols., 2007 (59)	1,227 subjects from 378 families with DM1 or DM2, concordant or discordant for DN	2q14.1, 7q21.1 and 15q26.3 7q21.3, 10p15.3, 14q23.1 and 18q22.3	Albuminuria Proteinuria or ESRD
Rogus and cols., 2008 (60)	Sibling concordant for DM1 and discordant for ND	19q, 2q and 3q 1q 20p	Proteinuria and ESRD ESRD Proteinuria
Pezzolesi and cols., 2009 (25)	Type 1 DM patients with DN (cases) and without DN (controls)	7p - CPVL/CHN2 9q - locus FRMD3 11p - locus CARS 13q	Proteinuria and ESRD

CKD: Chronic kidney disease; DM: *diabetes mellitus*; DN: diabetic nephropathy; DR: diabetic retinopathy; ESRD: end-stage renal disease.

- A genome-wide association study with 360,000 SNPs (using the microarray Affymetrix 5.0)was recently conducted in two independent cohorts of Caucasians patients with type 1 DM . SNPs that were highly significant in the two cohorts were selected for further analyses. Eleven SNPs located at 4 loci were closely associated with DN ($p < 1 \times 10\text{-}5$) .

Table 3. Single nucleotide polymorphisms associated with diabetic nephropathy in a population of GoKinD

SNP	Chromosome	Position (Mb)	Nearest gene	Risk Allele	Frequencies of risk alleles for cases and controls					
					GWU* GoKinD			JDC** GoKinD		
					Controls	Cases	p-value	Controls	Cases	p-value
N					413	379		472	441	
rs39059	7p	29.2	*CPVL/CHN2*	A(G)	0.61	0.69	8.8×10^{-4}	0.60	0.67	1.7×10^{-3}
rs39075	7p	29.2	*CPVL/CHN2*	G(A)	0.57	0.66	2.0×10^{-4}	0.57	0.64	8.2×10^{-4}
rs1888747	9q	85.3	*FRMD3*	G(C)	0.68	0.73	3.6×10^{-3}	0.66	0.74	4.4×10^{-5}
rs10868025	9q	85.4	*FRMD3*	A(G)	0.59	0.66	1.9×10^{-3}	0.56	0.66	7.2×10^{-5}
rs739401	11p	3.0	*CARS*	C(T)	0.46	0.54	4.7×10^{-4}	0.49	0.55	3.6×10^{-3}
rs451041	11p	3.0	*CARS*	A(G)	0.46	0.54	6.9×10^{-4}	0.48	0.56	1.3×10^{-3}
rs1041466	13q	109.0	No gene	G(A)	0.39	0.47	3.6×10^{-3}	0.43	0.51	2.7×10^{-4}
rs1411766/rs17412858	13q	109.1	No gene	A(G) G(A)	0.31	0.39	8.5×10^{-4}	0.32	0.40	6.4×10^{-4}
rs6492208/rs2391777	13q	109.1	No gene	T(C) G(A)	0.55	0.62	8.7×10^{-3}	0.56	0.65	1.9×10^{-4}
rs7989848	13q	109.1	No gene	A(G)	0.49	0.56	2.0×10^{-3}	0.50	0.57	1.1×10^{-3}
rs9521445	13q	109.1	No gene	A(C)	0.47	0.54	2.1×10^{-3}	0.47	0.55	4.2×10^{-4}

* GWU – George Washington University;
** JDC – Joslin Diabetes Center.

- these associations found in the cross-sectional study were confirmed in a prospective sample of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC).

- Three of the 11 initial SNPs had their association confirmed, two were borderline and the remaining did not show a significant association with the development of DN (proteinuria or CKD)

Single nucleotide polymorphisms associated with diabetic nephropathy in a population of *DCCT/EDIC*

SNP	Chromosome	Position (Mb)	Nearest gene	Risk allele	Allele frequency	p-value (unicaudal)	Hazard ratios
rs39075	7p	29.2	*CPVL/CHN2*	G	0.60	NS	0.85
rs1888746	9q	85.3	*FRMD3*	C	0.70	0.02	1.33
rs13289150	9q	85.4	*FRMD3*	A	0.62	0.05	1.23
rs451041	11p	3.0	*CARS*	A	0.51	0.01	1.32
rs1041466	13q	109.0	No gene	G	0.47	0.11	1.22
rs1411766	13q	109.1	No gene	A	0.36	0.11	1.17
rs6492208	13q	109.1	No gene	T	0.61	NS	0.90
rs7989848	13q	109.1	No gene	A	0.53	NS	0.93

- the studies using a GWS approach, a potential association was seen between chromosome 7q and phenotype of DN.

- Genes located in chromosomes 22q, 5q, and 7q might be involved in the determination of UAE severity in patients with and without DM.

- In a genome wide association study, regions in chromosomes 19 and 2q were identified as associated with proteinuria and ESRD in patients with type 1 DM .

- A locus in chromosome 1q was associated with ESRD only, while a locus in chromosome 20p was associated with proteinuria only .

Angiotensin II

Apo E

eNOS

Glut 1 polymorphism...

Table 7.1 Recent association studies of genetic polymorphism with diabetic nephropathy

Gene	Chromosome	Association
Angiotensin-converting enzyme (35, 38, 39)	17q	Controversial
Angiotensinogen (45)	1q	Controversial
Angiotensin II receptor 1 (45, 47, 48)	3q	Controversial
Aldose reductase (49–51)	7q	Controversial
Methylenetetrahydrofolate reductase (52, 53)	1p	Undetected
TGF-β1 (54)	19q	Undetected
Interleukin, receptor antagonist (55–57)	2q	Controversial
β3-adrenoceptor (58, 59)	8p	Controversial
G-protein β3 subunit (30)	12p	Undetected
ANP (60, 61)	1p	Controversial
Apolipoprotein E (62, 63)	19q	Requires confirmation
Collagen IV -α (64)	13q	Undetected
Kallikrein (65)	19q	Requires confirmation
Perlecan (66)	1p	Requires confirmation
Glucose transporter 1 (67)	1p	Requires confirmation
Preliminary genomic screening data (46)	3q, 7q, 9q, 20q	Requires confirmation

Benefit of identification of genes associated with DN

- Recognizing those individuals who are at high risk of developing this complication.
- It will also allow a better understanding of the mechanisms and progress of DN.
- Earlier and more aggressive therapies could be provided to high-risk individuals and thus reduce the associated high disease burden and mortality.
- Advances in pharmacogenetic research may help treatment choices by selecting renoprotective drugs according to individual susceptibility .

In conclusion

- Clinical and epidemiological studies have evidenced a genetic component of DN.
- However, no specific gene has been able to explain most DN cases
- Most genetic studies have been performed in selected populations but they are heterogeneous between them.
- Joint efforts are essential to achieve robust findings in the study of genetics of DN.

- future patients at high risk for developing DN could be identified and benefited with earlier specific therapies.

- New pharmacogenomic developments will contribute to better treatment choices for DN and, more importantly, will help preventing it based on an individual's genetic characteristics.

Thank you

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